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14. The method according to claim 8, wherein the polymethoxyflavone is obtained by:

subjecting a peel of a plant of the Genus Citrus of the Family Rutacea to extraction with at least one solvent selected from the group consisting of methanol, ethanol, propanol, butanol, ethyl acetate, acetone, propylene glycol, and 1,3-butylene glycol to obtain an extract (S1);

dissolving the extract (S1) in hexane and/or chloroform;

removing a precipitate from the hexane and/or chloroform solution;

distilling off the hexane and/or chloroform to obtain a dry solid product (S3); and

dissolving the dry solid product (S3) in a solvent, and subjecting it to liquid column chromatography.--

B3  
revised

#### REMARKS

Claims 1-14 are pending in the present application. Claim 1 has been amended to more particularly describe the cosmetic composition of the present invention. New claims 8-14 have been added to the application to separately claim the present method for whitening human skin. The amendments are supported at page 9, line 13, to page 12, line 27, of the specification. A reference cited in the specification has been corrected by amendment.

The present invention is directed to a cosmetic composition that includes a polymethoxyflavone and a whitening agent. The whitening agent may be one or more of ascorbic acid and its derivatives, hydroquinone and its derivatives, placental extracts, ellagic acid and its derivatives. The present cosmetic compositions are used for whitening skin.

Claim 2 was objected to by the Examiner because it did not include a period. Claim 2 has been amended to correct this deficiency.

Claims 1-3 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,792,448 to Dubief et al. (hereinafter "Dubief"). The Examiner asserts that

Dubief teaches the use of flavonoids for treating hair and that such hair treating compositions are cosmetic compositions encompassed by claims 1-3.

Dubief discloses the use of flavonoids for preserving and/or enhancing the mechanical properties of hair. Dubief further discloses a method for the preservation and/or enhancement of at least one mechanical property of hair, such as the mechanical properties tensile strength, breaking load, elasticity, or resistance to swelling in an aqueous medium. The Dubief method includes applying a cosmetically effective amount of a cosmetic composition that includes at least one flavonoid to hair for the purpose of protecting at least one of the mechanical properties.

Applicants have amended claim 1 and added new claims 8-14 in order to clearly describe the present invention and to make clear the differences between the claimed invention and that disclosed by Dubief. As currently amended, claim 1 includes features of the present invention not disclosed, or in any way suggested, by Dubief. The present cosmetic composition includes 0.00005 to 10 wt% of a polymethoxyflavone and 0.01 to 10 wt% of a whitening agent. The combination of the polymethoxyflavone and the whitening agent at the stated concentrations provides a synergistic whitening effect. This synergistic effect is described at page 12, lines 24-27, of the specification.

Furthermore, as described in new claims 8-14, the present invention relates to a method for whitening human skin using a cosmetic composition that includes one or more polymethoxyflavones. Dubief discloses treating hair and does not disclose or in any way suggest the present method for whitening human skin.

Dubief does not disclose or in any way teach the cosmetic composition of claims 1-3 or the method for whitening skin of claims 8-14. Dubief discloses a cosmetic composition for treating hair that includes 0.001 to 10 wt% of polymethoxyflavone. The

cosmetic composition including polymethoxyflavone for treating hair disclosed by Dubief is used to preserve and/or enhance the mechanical properties of hair.

Dubief does not disclose or suggest the composition comprising polymethoxyflavones and whitening agent of claims 1-3. Further, Dubief does not disclose or suggest the use of polymethoxyflavones as whitening agents for human skin. Moreover, Dubief does not describe or suggest the method for using polymethoxyflavones for whitening human skin as described in claims 8-14. Therefore, the rejection of claims 1-3 under 35 U.S.C. § 102(b) based on Dubief should be withdrawn.

Claims 4-7 stand rejected under 35 U.S.C. § 103 (a) for alleged obviousness over Machida et al. (Chem. Pharm. Bull., Vol. 37, No. 4, pp 1092-1094) in view of Williamson (Macroscale and Microscale Organic Experiments, 1989, pp. 116-118 and 152-153). The Examiner indicates his belief that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the extraction and eluent solvent system of Machida et al. by routine optimization as taught by Williamson in order to optimize the purification of polymethoxyflavones.

Machida et al. teaches ethanol extraction of a peel of a plant of genus Citrus and partitioning using ether. Williamson teaches general methods for isolating a substance.

The Examiner alleges that it would have been obvious to modify the extraction and eluent solvent systems of Machida et al. by routine optimization as taught by Williamson in order to optimize the purification of polymethoxyflavones as in the present invention. Applicants respectfully disagree.

There are many potential steps required for purifying a desired compound from a raw material. In the present invention, there are at least three steps. The first step is to extract a peel from a citrus plant with a solvent (1) so as to obtain a solid extract (X). The second step is to extract the solid extract (X) using a second solvent (2) to obtain a solid product (Y). The

third step is to dissolve the product (Y) in a third solvent (3) followed by chromatography on a column using a fourth solvent (4) to purify the polymethoxyflavone. It is well known to those skilled in the art that there are many solvent candidates for extracting a desired compound and that two or more solvents may be used in combination for extraction. It is also well known to those skilled in the art that the ratio of the combined solvents can affect the yield of the desired compound. Thus, there are an infinite number of candidate solvents for each step of an extraction and purification.

As stated above, there are at least three steps to purify polymethoxyflavone and solvents (1), (2), (3), and (4) are used in claims 4-7. Since each solvent (1)-(4) is selected from the infinite list of candidates respectively, the solvent system of claims 4-7 of the present invention is a result of only one combination selected from the infinite list of candidate solvents.

As described in claims 4 and 5, a feature of the present method is that a peel of a plant of genus Citrus can be extracted with a specific solvent; specifically, ethyl acetate (claim 4) or hexane and/or chloroform (claim 5) and subsequently subjected to liquid column chromatography. In particular, the liquid column chromatography is employed using silica and/or alumina and a solvent mixture of hexane/ethanol v/v 70/30 to 97/3 (claims 6 and 7). Neither Williamson nor Machida et al. describe or suggest the use of the solvents of claims 4-7.

Williamson merely teaches the principal of extraction. Machida et al. discloses extraction of polymethoxyflavones with ethanol and ether followed by gel chromatography using benzene-acetone. However, Machida et al. does not describe or teach the use of ethyl acetate or hexane/chloroform in the second step. Moreover, Machida et al. does not describe or teach the combination of solvents used in the first and second extraction steps and the solvent system of the gel chromatography step of the claimed invention.

The solvent system of claims 4-7 is a result of inventive efforts to discover extraction steps and specific solvent combinations from an infinite number of candidates.

Therefore, it would not have been obvious to those skilled in the art to select a specific solvent in the first step and ethyl acetate or hexane/chloroform for extraction in the second step.

Further, the solvent system and the ratio of the solvents in the solvent system used in column chromatography in claims 6 and 7, namely, hexane/ethanol v/v 70/30 to 97/3, are not disclosed or suggested by Machida et al. and/or Williamson. As described, it is very difficult to identify and not at all obvious to select the combination of solvents and ratio of solvents in the present invention.

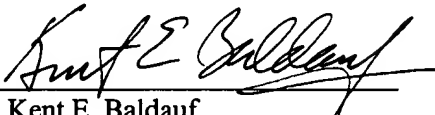
At best, the Examiner's position can be described as stating that it might have been obvious to try various solvents and solvent combinations from the infinite list of possible solvents to accomplish the present extraction method. "[T]he mere fact that a device or process utilizes a known scientific principle does not alone make that device or process obvious." In re Brouwer 77 F.3d 422, 425; 37 USPQ2D 1663 (Fed. Cir. 1995) quoting Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1053; 5 USPQ2D 1434, 1440 (Fed. Cir. 1988). Courts have consistently refused to recognize "obvious to try" rejections. "As we have said many times, obvious to try is not the standard of 35 USC 103." In re Tomlinson, 53 CCPA 1421, 363 F.2d 928; 150 USPQ 623 (CCPA 1966). "Disregard for the unobviousness of the results of 'obvious to try' experiments disregards the 'invention as a whole' concept of § 103." In re Antonie, 559 F.2d 618, 620; 195 USPQ 6, 8 (CCPA 1977)" (quoting In re Goodwin, 576 F.2d 375, 198 USPQ 1, 3 (CCPA 1978)). This view has been held consistently, as for example, In re Fine, 837 F.2d 1071; 5 USPQ2D 1596 (Fed. Cir. 1988) (but whether a particular combination might be 'obvious to try' is not a legitimate test of patentability).

Since the Examiner has failed to provide any motivation or suggestion based on the disclosures of Machida et al. and/or Williamson to arrive at the present extraction method, he has failed to provide a *prima facie* case. Accordingly, the rejection of claims 4-7 under 35 U.S.C. § 103 (a) should be withdrawn.

In view of the above amendments and remarks, reconsideration of the rejections  
and allowance of claims 1-14 are respectfully requested.

Respectfully submitted,

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**Marked-Up Version Paragraph**

**Second Full Paragraph on Page 15**

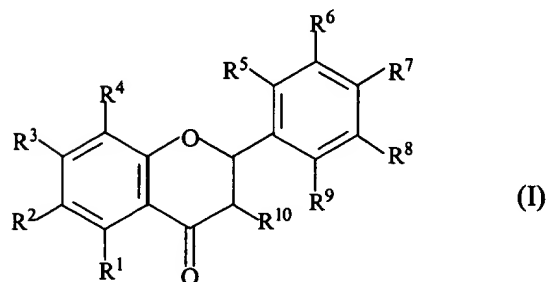
When these data are compared with the data described in references (Natural Medicines 51(3), 190-193\_(1997), Chem. Pharm. Bull. 37, 1092\_(1989), Pharmacological Magazine (YAKUGAKU ZASSHI) 116(3), 244-250 (1996) and Tetrahedron [, 16(8)] 8, 64\_(1964), the compound 2 was identified as 5,6,7,8,3',4'-hexamethoxyflavone (formula (III): nobiletin). The compound 3 was identified as 5,6,7,8,4'-pentamethoxyflavone (formula (IV): tangeretin).



### Marked-Up Versions of Claims 1 and 2

1. (Once Amended) A cosmetic composition comprising:

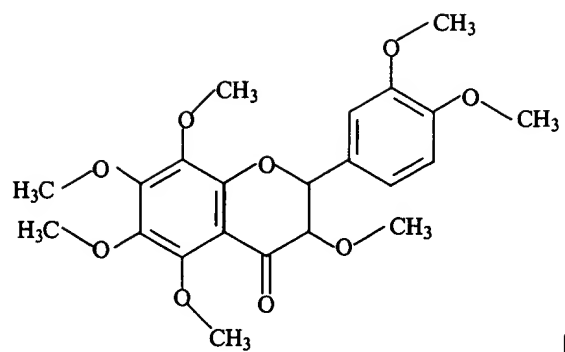
(a) 0.00005 to 10\_wt% of polymethoxyflavone represented by formula (I):



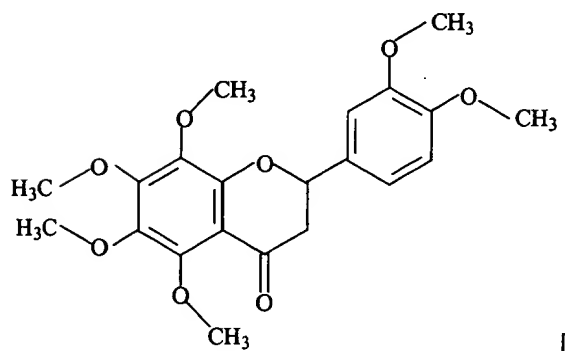
wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> is selected from the group consisting of hydrogen atom, hydroxyl group, alkoxy group having 1 to 20 carbon atoms, alkyl group having 1 to 20 carbon atoms, alkenyl group having 2 to 20 carbon atoms, hydroxyalkyl group having 1 to 20 carbon atoms or a sugar residue, and at least four of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> are methoxy groups; and

(b) 0.01 to 10 wt% of a whitening agent selected from the group consisting of ascorbic acid and its derivatives, hydroquinone and its derivatives, placental extracts, ellagic acid and its derivatives, and mixtures thereof.

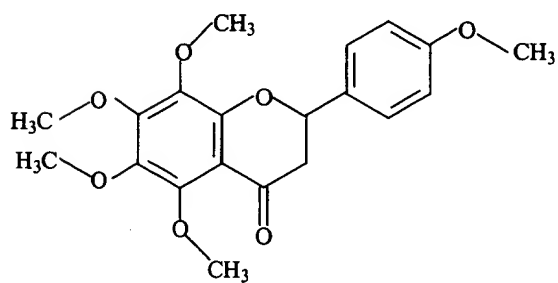
2. (Once Amended) The cosmetic composition of claim 1, wherein the polymethoxyflavone comprises at least one compound selected from the group consisting of [compounds represented by formulae (II) to (V):]



[(II)];



[(III)];



[(IV)]; and

